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[Intervention Review]

Penicillin for secondary prevention of rheumatic fever

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ABSTRACT

Background

People with a history of rheumatic fever are at high risk of recurrent attacks of rheumatic fever and developing rheumatic heart disease following a streptococcal throat infection. Giving penicillin to these people can prevent recurrent attacks of rheumatic fever and subsequent rheumatic heart disease. However, there is no agreement on the most effective method of giving penicillin.

Objectives

To assess the effects of penicillin compared to placebo and the effects of different penicillin regimens and formulations for preventing streptococcal infection and rheumatic fever recurrence.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (Issue 2, 2009), MEDLINE (1997 to June 2009), EMBASE (1998 to June 2009), LILACs (1980 to June 2009) and reference lists of articles. We contacted experts in the field.

Selection criteria

Randomised and quasi-randomised studies comparing (i) penicillin with control, (ii) oral with intramuscular penicillin (iii) 2- or 3-weekly with 4-weekly intramuscular penicillin in patients with previous rheumatic fever.

Data collection and analysis

Two reviewers independently assessed trial quality and extracted data.

Main results

Nine studies were included (n=3008). Data were not pooled because of heterogeneity. Overall, the methodological quality of included studies was poor. Three trials (n= 1301) compared penicillin with control. Only one of three studies showed that penicillin reduced rheumatic fever recurrence (RR 0.45, 95% CI 0.22 to 0.92) and streptococcal throat infection (RR 0.84, 95% CI 0.72 to 0.97). Four trials (n=1098) compared intramuscular with oral penicillin and all showed that intramuscular penicillin reduced rheumatic fever recurrence and streptococcal throat infections compared to oral penicillin. One trial (n= 360) compared 2-weekly with 4-weekly intramuscular penicillin. Penicillin given every two-weeks was better at reducing rheumatic fever recurrence (RR 0.52, 95% CI 0.33 to 0.83) and streptococcal throat infections (RR 0.60, 95% CI 0.42 to 0.85). One trial (n= 249) showed 3-weekly intramuscular penicillin injections reduced streptococcal throat infections (RR 0.67, 95% CI 0.48 to 0.92) compared to 4-weekly intramuscular penicillin.

Authors' conclusions

Intramuscular penicillin seemed to be more effective than oral penicillin in preventing rheumatic fever recurrence and streptococcal throat infections. Two-weekly or 3-weekly injections appeared to be more effective than 4-weekly injections. However, the evidence is based on poor quality of trials.

PLAIN LANGUAGE SUMMARY

Penicillin reduces the risk of streptococcal throat infections and attacks of rheumatic fever in people who have already had a bout of rheumatic fever

Rheumatic fever is a rare complication of throat infection, that can damage the heart. People who have had rheumatic fever can suffer from it again following streptococcal throat infection if they do not receive regular penicillin. Penicillin for prevention can be given by injection or as tablets. Taking tablets is easier but might not work as well as injections. The review of trials compared different ways of giving penicillin. Penicillin seemed to work better as injections than as tablets. Injections given every two or three weeks worked better than when given every four weeks. However, more research is needed.

BACKGROUND

Rheumatic fever is the most important cause of acquired heart disease in children and young adults worldwide. It is an inflammatory reaction that occurs approximately 10 to 21 days after throat infection with virulent strains of Group A beta-haemolytic streptococci. It affects large joints (arthritis), the heart (carditis) and less frequently the brain (chorea), skin (erythema marginatum) and subcutaneous tissues. Rheumatic heart disease refers to the functional and structural changes of the heart muscle and valves affected by rheumatic fever. Rheumatic fever has a marked tendency to recur following new group A streptococcal upper respiratory tract infection. Recurrence has a high risk of chronic heart lesions or worsening lesions in patients with previous rheumatic heart disease. The severity of rheumatic heart disease and the prognosis depend on the extent of the carditis and the frequency of recurrent attacks. There is much evidence from randomised controlled trials concerning the primary prevention of rheumatic fever or the treatment of pharyngitis caused by Group A beta-haemolytic streptococci (GAS) but less data is available concerning secondary prevention of the disease.

Epidemiology

Worldwide, over 12 million people are affected by rheumatic fever and rheumatic heart disease and about 400 000 deaths result from rheumatic heart disease annually (WHO/ISFC 1995). The occurrence of rheumatic fever has declined dramatically in developed countries over the last 100 years to a prevalence of 0.6-0.7 per 1000 population in the USA and Japan (Brice 1998), although isolated outbreaks have been reported in affluent communities in the United States in recent times (Veasey 1987). The prevalence of rheumatic fever and rheumatic heart disease is high in areas with poor socioeconomic conditions, overcrowding and limited access to medical care (Longo-Benza 1998). The reduction in prevalence of rheumatic fever in developed countries preceded the introduction of antibiotics and is probably related to the improvement in these non-medical factors.

In contrast, rheumatic fever remains a major cause of acquired heart disease in developing countries and poor communities (Agarwal 1981; Hakim 1998; Mayosi 1996) where rheumatic heart disease prevalence rates of 19.2-24 per 1000 have been reported (Carapetis 1996; McLaren 1975). It has been estimated that in developing countries almost twice as many children have rheumatic valvular heart disease as congenital heart disease, a pattern that was observed in the United States over 40 years ago (Kaplan 1993). In these countries rheumatic fever occurs in a much younger age group than in developed countries and severe chronic valvular heart disease develops early (Halim 1961; Padmavati 1978). The option of valve replacement is not available in most instances. As a result rheumatic fever and rheumatic heart disease cause serious disability, premature death and significant healthcare expenditure in developing countries.

Rheumatic fever complicates untreated by Group A beta-haemolytic streptococcal infection in 0.1 to 0.3% in the general population and 3% in epidemics in closed communities (Siegel 1961). However, the incidence of rheumatic fever following GAS infection rises to 50% in those with a previous experience of rheumatic fever. This underscores the importance of secondary prevention in individuals with a previous history of rheumatic fever.

Prevention

Prevention of rheumatic fever may be considered to be prevention of the initial attack (primary prevention) or prevention of recurrent attacks (secondary prevention). It has been argued that true primary prevention of rheumatic fever depends more on improvement of socioeconomic factors and education directed at the public and health workers (Bach 1996) than provision of antibiotics. However, a primary prevention programme of parenteral penicillin treatment for all streptococcal throat infections instituted in Costa Rica in the 1970's was successful in eliminating rheumatic fever (Arguedas 1992). The subject of primary prevention of rheumatic fever and treatment of streptococcal sore throat has been reviewed recently (Del Mar 2006; Zwart 2000).

Secondary prevention is particularly important since even an asymptomatic or optimally treated GAS throat infection can still trigger rheumatic fever recurrence. Therefore concentrating on prompt diagnosis and treatment of streptococcal throat infections on its own is not adequate. The options for secondary prevention are the use of a vaccine against GAS and antibiotic chemoprophylaxis. Unfortunately, the availability of a vaccine is still several years away and antibiotic chemoprophylaxis is the only option available at the moment. There is data to suggest that continuous regular antibiotic prophylaxis can prevent or significantly reduce the development of valvular damage, the prevalence of rheumatic heart disease with disappearance of pre-existing heart murmurs (Stollerman 1955; Thompkins 1972) and reduction in mortality (Majeed 1992). The importance of secondary prevention is well appreciated and several programmes have been established in developing countries (WHO 1992).

The most recent recommendations on the secondary prevention of rheumatic fever have been published by the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease of the Council on Cardiovascular Disease in the Young (AHA 1956) (Dajani 1995) and the World Health Organisation (WHO 1988). Both recommend penicillin as the drug of choice for secondary prevention, given as daily oral tablets or as 3-weekly or 4-weekly intramuscular injections. Three-weekly injections are recommended in areas with a high incidence of rheumatic fever or in high-risk groups. This recommendation is based on pharmacokinetic data (Currie 1994; Kaplan 1989; Meira 1993) and results of trials and observational studies (Daniels 1994; Lue 1996; Padmavati 1987;).

The wide choice of penicillin regimens given in current recommendations indicates the uncertainty and controversy regarding the most effective regimen for secondary prevention of rheumatic fever. Some authorities consider intramuscular injections of benzathine penicillin to be more effective than tablets taken every day (Anonymous 1999; Dajani 1995; WHO 1988). However, due to the perceived higher risk of anaphylaxis and the dangers associated with the reuse of needles still practiced in some poor communities and the discomfort of intramuscular injections, there is resistance to the use of intramuscular penicillin. The safety issues regarding the use of penicillin injections have resulted in government orders prohibiting penicillin injections in hospitals and clinics (Padmavati 2001).

The aim of this review is to summarise the evidence for the use of penicillin for the secondary prevention of rheumatic fever and to identify the most effective penicillin regimen. This information will

be of help to policy makers, health practitioners and researchers in this area.

OBJECTIVES

To examine the effects of penicillin compared to control and the effects of different penicillin regimens and formulations for preventing streptococcal infection and rheumatic fever recurrence.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials of at least 6 months duration. Non-randomised or poorly randomised studies were included if a control or comparison group was specified.

Types of participants

Children and adults with a history of rheumatic fever with or without current evidence of rheumatic heart disease, with the initial diagnosis of rheumatic fever based on the Jones criteria (Jones 1944), modified Jones criteria (AHA 1956) and revised Jones criteria (Dajani 1992).

Types of interventions

Selected studies were those in which the following interventions were compared:
(1) penicillin (oral or intramuscular) versus control;
(2) daily oral penicillin versus intramuscular penicillin;
(3) 2-weekly or 3-weekly versus 4-weekly intramuscular penicillin.

Types of outcome measures

Primary outcomes: rheumatic fever recurrence, mortality related to rheumatic fever and rheumatic heart disease and development of chronic rheumatic heart disease.
Secondary outcomes: streptococcal throat infections, compliance and adverse events.

Search methods for identification of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (Issue 2, 2009), MEDLINE (1997 to June 2009), EMBASE (1998 to June2009), LILACs (1980 to June 2009). See Appendix 1 for details of search strategies. Reference lists of identified articles were checked. We contacted experts in the field for unpublished or ongoing studies (see additional Table 1). No language restrictions were applied.

Data collection and analysis

Applying inclusion criteria

Two hundred and fifty six (256) citations were retrieved from the databases and two reviewers independently assessed their titles and abstracts for possible inclusion. The reviewers were not be blinded to the journal, institution or results of the study. Differences on whether trials met the inclusion criteria were resolved by discussion.

Assessment of quality of studies

Studies fulfilling inclusion criteria were appraised independently by the two reviewers. The study characteristics and outcome measures were abstracted onto a pre-designed data-extraction form. The aspects used to assess the quality of included studies were the method of randomisation, adequacy of concealment of treatment allocation and the rate of completion of follow up.

Data analysis

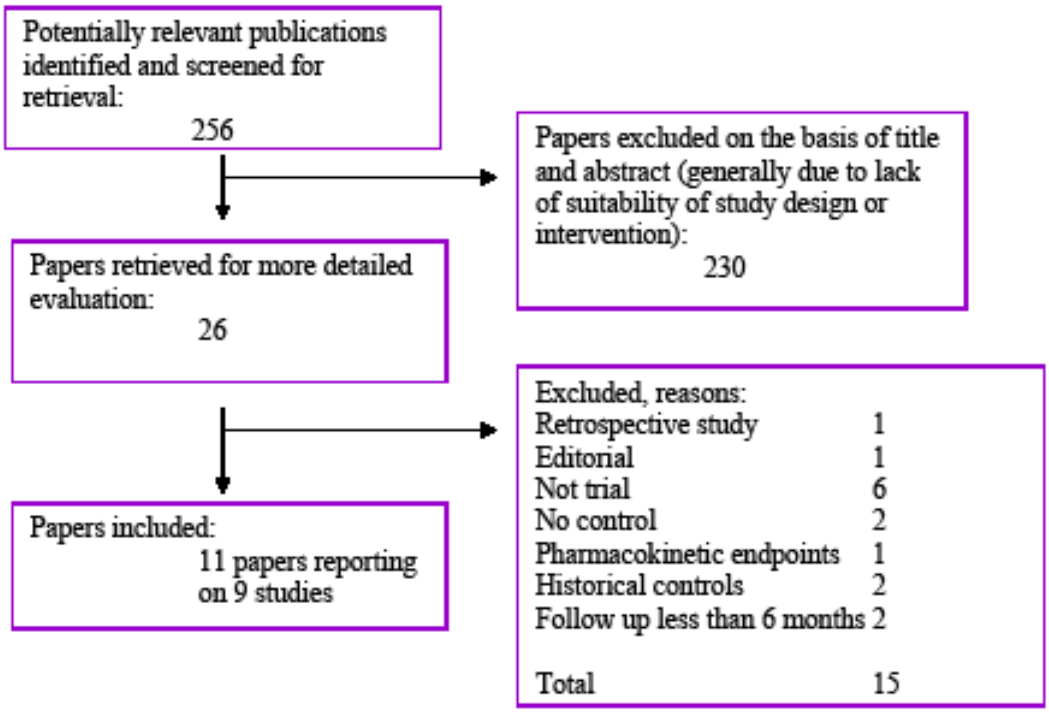
For each study the outcomes were summarised into relative risks and 95% confidence intervals (CI). The chi-squared heterogeneity test as well as visual inspection of the graphs were used to test for homogeneity between the studies and a significance level of less than 0.10 interpreted as evidence for heterogeneity. The plan was to analyse data initially using the fixed effects model and to reanalyse using the random-effects model in the presence of heterogeneity. However, because of differences in methodology and study populations data were not pooled. Reasons for the heterogeneity were explored.

RESULTS

Description of studies

For further description of the studies please see the Characteristics of included studies and Characteristics of excluded studies tables and the QUOROM statement flow diagram (Figure 1).

Figure 1. QUOROM statement



Excluded studies

Two hundred and fifty six (256) potentially relevant citations were retrieved through the search strategy and 230 of these were excluded on the basis of title and abstract. Twenty six papers were retrieved for more detailed evaluation. Fifteen of these were excluded for the following reasons; not trials (6), editorial on primary prevention (1), retrospective study (1), trials comparing penicillin with another antibiotic (2), pharmacokinetic outcomes (1), use of historical controls (2), follow-up period less than 6 months (2).

Nineteen experts were contacted for additional references (please see additional Table 1) and no additional published or unpublished studies were identified this way.

Included studies

Nine studies (reported in eleven papers) were included in this review. We grouped the studies into those comparing penicillin with control (3 randomised trials, 1301 patients), oral with intramuscular penicillin (4 randomised trials, 1098 patients), 2-weekly with 4-weekly penicillin injections (1 randomised trial, 360 patients) and 3-weekly with 4-weekly intramuscular penicillin injections (1 randomised trial, 249 patients). The trial durations ranged from 1 to 12 years. Overall most studies were of sub-optimal quality, with use of inadequate randomisation and in all studies there was no indication that outcome assessors were blinded. The studies also differed in the baseline risks of rheumatic fever.

Participants

The ages of children in 3 of the studies were not specified (Feinstein 1959; Kohn 1953; Padmavati 1973). In the remaining studies the ages of the participants ranged from 3 to 24 years. Manifestations of rheumatic fever in the previous attack were not uniform with some having presented with carditis but with no residual rheumatic heart disease, some having presented with arthritis, while a few had had chorea. Patients were followed up every month or every 2 months at which time they were assessed for clinical, bacteriological and serological markers of rheumatic fever recurrence and streptococcal throat infection.

Measurement of outcomes

Rheumatic fever recurrence: The basis for diagnosing rheumatic fever was the Jones criteria in the earliest study (Kohn 1953), modified Jones criteria in (Feinstein 1959; Feinstein 1965; Feinstein 1966; Feinstein 1968; Padmavati 1973; Wood 1964) and the revised Jones criteria for the latest studies (Kassem 1996; Lue 1996).

Streptococcal throat infections: Streptococcal throat infections were reported as either clinical infection, positive throat culture or raised serological markers. The serological test done initially was antistreptolysin O titre (ASOT). In cases where throat culture and ASOT were positive, serial ASOT, hyaluronidase and antistreptokinase were taken. In our data extraction, we took positive throat culture and serology as evidence for streptococcal throat infection. This was based on the fact that a positive throat culture on its own may be due to throat carriage without infection.

Compliance: This was assessed by one or all of the following means: interview, tablet counts or average number of injections missed. However, although six of the studies assessed compliance, only two reported this outcome (Lue 1996; Wood 1964).

Risk of bias in included studies

Randomisation, blinding and allocation concealment

Overall, the methodological quality of included studies was poor. Treatment allocation was not adequately described in 3 studies (Feinstein 1959; Feinstein 1965; Feinstein 1968) and was not described at all in 2 studies (Kassem 1996; Kohn 1953). The other methods of treatment allocation were dependent on the day of the week the patient was seen (Padmavati 1973) or on odd or even hospital numbers allocated in an alternating sequence (Feinstein 1966). The study by Lue et al. (Lue 1996) is reported as 3 separate publications and summarises results of a 12-year prospective follow-up study. Allocation to intervention group was initially done on the basis of odd or even hospital numbers but children recruited between 1985 and 1991 were allocated on the basis of random permutations. It was not possible to sort out results by method of treatment allocation.

In the later study of Feinstein (Feinstein 1968), 216 of the 343 patients were admitted from the previous trial (Feinstein 1965) and they stayed in the groups to which they had been previously allocated. In the study by Feinstein et al. (Feinstein 1965), seventeen patients initially allocated to intramuscular penicillin were transferred to oral penicillin because they were not willing to continue receiving injections. This would have introduced contamination. The outcomes of these patients were not given separately, so it was not possible to perform intention-to-treat analysis.

Blinding is not possible when injections are compared to oral tablets and in all comparisons the authors do not indicate whether outcome assessment was blind.

Completion of follow-up

Follow up completion was not reported consistently in the studies. Padmavati et al. (Padmavati 1973) reported a 25.8% drop out rate. In the study Lue 1996, of the 267 patients initially randomised, 18 were lost to follow up and were not accounted for in the final result.

Effects of interventions

Please see list of comparisons and figures. Nine studies were included (n=3008). Three trials (n= 1301) compared penicillin with control, 4 trials (n= 1098) compared intramuscular with oral penicillin, 1 trial (n= 360) compared 2-weekly with 4-weekly intramuscular penicillin and 1 trial (n= 249) compared 3-weekly with 4-weekly intramuscular penicillin. There was no statistical heterogeneity between the studies. However, the results were not pooled because of differences in trial methodologies and the patient characteristics across studies.

Oral or intramuscular penicillin versus control

One thousand three hundred and one (1301) patients were included in the three studies, 645 receiving penicillin and 656 receiving no preventive treatment (Feinstein 1966; Kohn 1953; Padmavati 1973). Results from all three studies showed 15 rheumatic fever recurrences among patients receiving penicillin and 43 among those receiving control, in total. Penicillin reduced the risk of rheumatic fever recurrence by 55% compared to control in one study (RR 0.45, 95% CI 0.22 to 0.92) (Padmavati 1973). Streptococcal throat infections were reduced by 16% in the penicillin-treated group (RR 0.84 and 95% CI 0.72-0.97) (Padmavati 1973). The other 2 studies showed similar results but the differences were not statistically significant. One study reported no significant difference in mortality due to progression of heart failure or acute carditis (RR 1.52, 95%CI 0.78 to 2.99) and all-cause mortality (RR 1.23, 95%CI 0.78 to 1.94) between the penicillin and control groups (Padmavati 1973). The other studies did not report on mortality.

Intramuscular versus oral penicillin

One thousand and ninety-eight (1098) patients were included in the four studies, 561 receiving intramuscular penicillin and 537 receiving oral penicillin. There were 7 rheumatic fever recurrences among patients receiving intramuscular penicillin and 89 among patients receiving oral penicillin. All four studies showed a reduction in the risk of rheumatic fever recurrence in patients receiving intramuscular penicillin compared to those receiving oral penicillin (Feinstein 1959: RR 0.06, 95% CI 0.01 to 0.48; Feinstein 1965; RR 0.04, 95% CI 0.01 to 0.30; Feinstein 1968: RR 0.13, 95% CI 0.04 to 0.41; Wood 1964: RR 0.07, 95% CI 0.02 to 0.27). There were 78 streptococcal throat infections among patients receiving intramuscular penicillin and 313 among those receiving oral penicillin. Three studies showed significant reduction in streptococcal infection in the intramuscular regimen compared to the oral regimen (Feinstein 1968: RR 0.29,95% CI 0.21 to 0.40; Feinstein 1965: RR 0.09, 95% CI 0.05 to 0.17; Wood 1964: RR 0.23, 95% CI 0.16 to 0.34).

Two-weekly versus 4-weekly intramuscular penicillin

Three hundred and sixty (360) patients were included in one study, 190 receiving 2-weekly injections and 170 receiving 4-weekly injections (Kassem 1996). There were 24 rheumatic fever recurrences among patients receiving 2-weekly injections and 41 among those receiving 4-weekly injections (RR 0.52, 95% CI 0.33 to 0.83). There were 38 streptococcal infections in the 2-weekly treated group and 57 in the 4-weekly treated group (RR 0.60, 95% CI 0.42 to 0.85).

Three-weekly versus 4-weekly intramuscular penicillin

This comparison was made in one study with two hundred and forty nine (249) patients, 124 receiving 3-weekly injections and 125 receiving 4-weekly injections (Lue 1996). There were 9 rheumatic fever recurrences in the 3-weekly treated group and 16 in the 4-weekly treated group but this difference did not reach statistical significance (RR 0.57, 95% CI 0.26 to 1.23). There were 39 streptococcal throat infections among children receiving 3-weekly injections and 59 among those receiving 4-weekly injections (RR 0.67, 95% CI 0.48 to 0.92). This study also reported patient compliance with three-weekly and four-weekly injection programs to be comparable.

Methodological quality and treatment effects

When the results are compared according to methodological quality, there was no consistent pattern of poor quality studies showing a greater or lesser effect size than better designed studies.

Other outcomes

Only one study reported on mortality (Padmavati 1973). Adverse events were not presented uniformly in the studies. Wood and others provide 8-year follow up data on cardiac sequelae and mortality for the entire group but it is not presented separately for each intervention group (Wood 1964).

Publication bias

Efforts to identify unpublished literature through contacting experts in the field did not increase the yield. With only three studies in the comparison between penicillin and placebo, four comparing intramuscular and oral penicillin, one comparing 3-weekly with 4-weekly penicillin injections and one comparing 2-weekly with 4-weekly injections, it was not possible to look for publication bias from funnel plots.

DISCUSSION

Findings

There are three principal findings of this review. Firstly, the available evidence is in favour of penicillin compared to no treatment in the prevention of repeated attacks of rheumatic fever. One of three studies comparing penicillin to no preventive treatment showed a 55% reduction in the recurrence of rheumatic fever (Padmavati 1973), whilst the other two revealed a non-significant trend in favour of penicillin (Feinstein 1966; Kohn 1953). Secondly, the evidence seems to be even stronger for intramuscular versus oral penicillin where all the four studies showed a 87% to 96% reduction in rheumatic fever recurrence (Feinstein 1959; Feinstein 1965; Feinstein 1968; Wood 1964) and a 71% to 91% reduction in streptococcal throat infection (Wood 1964; Feinstein 1965, Feinstein 1968). Thirdly, the evidence from this review suggests that more frequent injections are more effective in preventing rheumatic fever recurrence than 4-weekly injections. This evidence is strong for 2-weekly injections with an almost 50% reduction in the risk of rheumatic fever recurrence and a 40% reduction in streptococcal throat infections compared to 4-weekly injections (Kassem 1996). The evidence for 3-weekly injections is less strong and may be even weaker if we take into account the systematic error introduced by inadequate randomisation and allocation concealment in the study by Lue and others (Lue 1996).

However, for all comparisons, the evidence is based on studies that were not properly randomised. This may have resulted in bias in treatment allocation. The effect of this would be to exaggerate the true effect of penicillin and of injections compared to tablets. Furthermore, there was marked variation in terms of the geographical areas, time periods and more importantly, the trial methodologies and penicillin dosage schedules used in the various studies.

Types of interventions

The oral penicillin doses and schedules differed between the studies. In three studies penicillin tablets were given every day (Feinstein 1959, Feinstein 1966, Feinstein 1968), in one study tablets were given during the first 7 days of every month (Kohn 1953), in one study tablets were given only during the first 10 days of every month (Feinstein 1965) and in one study penicillin or another antibiotic was given as and when necessary for streptococcal throat infections (Padmavati 1973). The earlier studies used an old preparation of penicillin, potassium penicillin G (Feinstein 1959; Feinstein 1965; Feinstein 1968). Phenoxymethyl penicillin (penicillin V), the oral penicillin preparation used today, is more consistently absorbed and produces high blood levels. There is evidence to suggest that this form of penicillin results in low frequency of rheumatic fever recurrence comparable with benzathine penicillin (Phair 1973). Therefore results drawn from this review may not apply to current oral penicillin preparations.

Taking tablets is more convenient for patients. However, it is easier to ensure compliance with medication administered by injection. It is therefore possible that the better results with injections were simply because this route of penicillin administration assured compliance.

Outcomes reported

All studies reported streptococcal throat infections and rheumatic fever recurrence. Rheumatic fever recurrence was diagnosed using the widely accepted Jones criteria (AHA 1956; Dajani 1992; Jones 1944). The trials provided data on serological markers of streptococcal throat infection (antistreptolysin O, antistreptokinase and hyaluronidase). Serological markers on their own do not confirm infection. In this review a diagnosis of streptococcal throat infection was based on the combination of a positive throat culture and a rise in any of the serological markers. This made it possible to differentiate throat carriage and true streptococcal throat infections.

One limitation of this review is the lack of data on the clinically relevant outcomes of disappearance of heart murmurs, resolution of valve lesions, mortality due to heart failure and adverse events. Observational studies suggest that oral penicillin is safer than parenteral penicillin in terms of allergic and anaphylactic reactions (Idsoe 1968). The International Rheumatic Fever Study Group, a prospective cohort study from 11 developing countries, showed a 0.2% incidence of anaphylactic reactions with a fatality rate of 0.05% (IRFSG 1991). When viewed in the light of the evidence in favour of penicillin injections from this review, this data suggests that the long-term benefits of prophylactic penicillin injections outweigh the risks.

Generalisability

Studies included in the review were conducted in Africa (Kassem 1996), Asia (Lue 1996; Padmavati 1973) and the United States of America (Feinstein 1959; Feinstein 1965; Feinstein 1966; Feinstein 1968; Kohn 1953; Wood 1964). The baseline risks of rheumatic fever were different depending on the geographical area, time period when studies were conducted and host factors in the populations studied and the inclusion criteria used in each study. This would limit applicability of the results in general.

AUTHORS' CONCLUSIONS

Implications for practice

Intramuscular penicillin seemed to be more effective than oral penicillin in preventing rheumatic fever recurrence and streptococcal throat infections. Two-weekly or 3-weekly injections appeared to be more effective than 4-weekly injections. Even though trials in this review were of poor quality, the evidence is quite strong and it is reasonable to promote current guidelines which are based on this evidence until further evidence becomes available. There have been anecdotal reports of sudden deaths following benzathine penicillin injections given to people with no prior history of penicillin allergy. In some communities this has led to the public and health care workers to prefer oral penicillin. If current guidelines for rheumatic fever secondary prevention are to be implemented, the safety and quality of penicillin injections needs to be assured. Public health education attempts should focus on increasing awareness among patients with rheumatic fever on

the need for regular continuous antibiotic prevention and to inform them of the options available.

Implications for research

1.In view of the poor quality of the available evidence, well-designed randomised controlled trials comparing the effectiveness of penicillin injections with oral phenoxymethylpenicillin are required. Such studies should be of long duration to allow them to measure the clinically important outcomes of resolution of heart murmurs, improvement in signs and symptoms of heart failure and reduction in mortality and cost-effectiveness of the different treatment regimens.

2.Pharmakokinetic studies have demonstrated that penicillin injections given every 2 or 3 weeks ensure penicillin levels above minimum inhibitory concentration (Kaplan 1989; Meira 1993; Stollerman 1952). These findings are in support of the 2-weekly or 3-weekly injections. There is still a need for well-designed multi-centre randomised controlled trials to compare 2-weekly, 3-weekly and 4-weekly penicillin injections.

3.Regarding the safety of intramuscular penicillin, there is need to set up surveillance and adverse drug reactions monitoring systems. Penicillin injections administered with a local anaesthetic cause less discomfort and there is a suggestion that it may be associated with fewer sudden deaths. This is a question that also needs to be addressed in future trials.

4.Patients with rheumatic fever and their families should be involved in discussions to set research priorities that answer questions relevant to their needs.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Feinstein 1959

Methods	Patients were divided into 3 groups by a 'statistical randomisation method'.
Participants	391 patients with rheumatic fever. Mean age was not specified.
Interventions	1.Sulphadiazine 1g orally once daily. 2.Potassium

Feinstein 1959 *(Continued)*

	penicillin G 200 000U orally once daily 3.Benzathine penicillin G 1.2MU i.m. 4weekly.
Outcomes	Streptococcal throat infections Rheumatic fever recurrence
Notes	Baseline characteristics not tabulated but groups said to be comparable in age, cardiac status and duration of freedom from rheumatic activity. Study duration 3 years

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Feinstein 1965

Methods	Patients were divided into 2 groups by a 'special statistical technique'.
Participants	237 patients 5-16 years old with rheumatic fever.
Interventions	Benzathine penicillin G 1.2MU i.m. monthly 2. Potassium penicillin G 400 000U 3 times a day for 10 days and patients were not on prophylactic treatment for the rest of the month.
Outcomes	Streptococcal throat infections Rheumatic fever recurrence
Notes	Study terminated prematurely because of marked superiority of benzathine penicillin. 17 of the 119 children initially randomised to i.m. benzathine penicillin G were later transferred to oral penicillin. Study duration was 2 years

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	C - Inadequate

Feinstein 1966

Methods	Boxes were marked "E" (for even) and "O" (for odd) and the prophylaxis preparation was assigned in alternating sequence as each patient was admitted to the study. Not clear if observers were blinded.
Participants	161 patients 14-24 years old with history of rheumatic fever but at low risk of rheumatic fever recurrence.
Interventions	Prophylaxis group received potassium penicillin G 200 000 units once daily. The control group received 1 tablet of placebo daily.
Outcomes	Rheumatic fever recurrence Streptococcal throat infections

Feinstein 1966 *(Continued)*

Notes	Low baseline risk of RFR in the population studied. Those at risk of recurrences were excluded from the study. Study duration was 2 years.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	C - Inadequate

Feinstein 1968

Methods	Patients were from 2 different sources; one group continued from the 1965 study , other group was new recruits who were divided into 2 groups by a 'special statistical technique'.
Participants	343 patients 5-17 years old with rheumatic fever.
Interventions	1.Benzathine penicillin G 1.2MU i.m. monthly 2.Potassium penicillin G 400 000U orally 3 times a day for 10 days then 400 000U once daily for the rest of the month.
Outcomes	Streptococcal throat infections Rheumatic fever recurrence
Notes	Not clear whether observers were blinded. Duration of study was 4 years.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	C - Inadequate

Kassem 1996

Methods	Patients were randomly assigned to either a bi-weekly (190) or 4-weekly (160) prophylaxis program.
Participants	360 patients 4-20 years old.
Interventions	1. Benzathine penicillin G i.m. 2-weekly. 2.Benzathine penicillin G i.m. 4weekly
Outcomes	Streptococcal throat infections Rheumatic fever recurrence
Notes	The authors do not give adequate detail on baseline characteristics but they state that the 2 prophylaxis groups had comparable age, sex ratio and were more or less matched with regard to social status, initial diagnosis and duration of rheumatic fever. Study duration was 2 years.

Risk of bias

Bias	Authors' judgement	Support for judgement

Kassem 1996 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	B - Unclear

Kohn 1953

Methods	Method of treatment allocation not specified, not a clear whether this was a randomised trial, unclear whether study was blinded.
Participants	157 patients, 40 in the prophylaxis group, 60 in control group 1 and 57 in control group 2.
Interventions	Prophylaxis group received penicillin 800 000 units daily for 7 consecutive days of the first week of each month. Control group 1 received no prophylaxis but attended the same school as the children receiving prophylaxis. Control group 2 received no prophylaxis and attended a different school to those who were receiving prophylaxis.
Outcomes	Rheumatic fever recurrence
Notes	Results of streptococcal throat infections not provided. There was contamination in control group 2 where 11 of the children received antibiotics independently prescribed by their family doctors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Lue 1996

Methods	Allocation to treatment group from 1971-1984 was done on the basis of odd or even hospital numbers. Allocation to treatment group was by random permutations from 1985 to1991.
Participants	249 patients 3-19 years old, male : female ratio 1.1.
Interventions	1. Benzathine penicillin G i.m. 3-weekly. 2.Benzathine penicillin G i.m. 4 weekly
Outcomes	Streptococcal throat infections Rheumatic fever recurrence
Notes	Duration of follow up was 12 years. The paper summarises the results of the 12-year prospective follow-up study which is reported at different stages as 3 separate publications (Lue et al, 1986; Lue et al, 1994; Lue et al., 1996). Patients were initially studied in the cardiac clinic but during the course of the study, about 50% of them were followed up in the rheumatic fever clinic. Fourteen were excluded within 2 months of entry into the study (8 drop outs and 6 deaths).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	C - Inadequate

Padmavati 1973

Methods	Treatment allocation depended on the day of the week that the patient presented to hospital. It was an open study.
Participants	Started with 944 patients, 10-19 years old, 523 in the prophylaxis group and 471 in the control group. 577 were regular in attendance.
Interventions	Patients were divided into 2 groups; the prophylaxis group receiving benzathine penicillin G injections (dose not specified) once a month and the control group receiving monthly vitamin B injection and penicillin or other antibiotics as and when necessary for streptococcal throat infections.
Outcomes	Rheumatic fever recurrence Streptococcal throat infections
Notes	Results are given for the 577 who were regular and not lost to follow up (58% of those randomised). Chronic valvular disease was present in the majority of subjects. High baseline prevalence of rheumatic heart disease in the population studied. Patients were followed up for 5 years. Streptococcal infection data was difficult to interpret since it was reported as throat and nasal culture results combined as well as antistreptolysin O titres.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Wood 1964

Methods	Patients were assigned to treatment group using consecutively numbered envelopes with drugs allocated by a statistical table of random numbers.
Participants	431 patients, 5-18 years old.
Interventions	1. Benzathine penicillin G injections 1.2 MU every 4 weeks 2 (146 patients). 2. Oral penicillin G 200 000 units once daily (143 patients) 3. Sulphadiazine 1 g once daily (142 patients)
Outcomes	Streptococcal throat infections. Rheumatic fever recurrences.
Notes	Mean duration of follow up 3.6 years.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adam 2000	Not a trial. An introduction to a symposium
Anonymous 2000	A narrative review
Bavdekar 1999	Not a trial
Brick 1950	Non-randomised, no description of control treatment
Carapetis 1998	Editorial emphasising on primary prevention
Denbow 1999	A non-randomised comparison of penicillin versus no prophylaxis in a pair of monozygotic twins
El Kholy 1980	Not a secondary prevention trial
Feinstein 1964	Comparison of penicillin with sulphadiazine
Gebremariam 1999	Used historical controls
Ghram 1999	A retrospective study
Kotby 1998	Follow up period less than 6 months
Massell 1979	comparison of penicillin with clindamycin
Padmavati 1987	Used historical controls
Stollerman 1952	Follow up period 2 to 10 months
Thamlikitkul 1992	Pharmacokinetic study of rheumatic fever preventive regimens

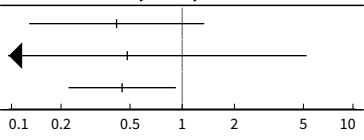
DATA AND ANALYSES

Comparison 1. Oral or intramuscular penicillin versus control

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Rheumatic fever recurrences	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Streptococcal throat infections	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 All Cause Mortality	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Mortality due to progress of heart failure or carditis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

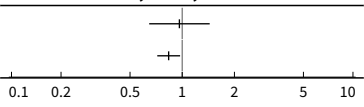
Analysis 1.1. Comparison 1 Oral or intramuscular penicillin versus control, Outcome 1 Rheumatic fever recurrences.

Study or subgroup	Penicillin n/N	Placebo / Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kohn 1953	3/40	19/106		0.42[0.13,1.34]
Feinstein 1966	1/82	2/79		0.48[0.04,5.21]
Padmavati 1973	11/523	22/471		0.45[0.22,0.92]



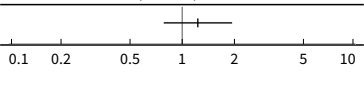
Analysis 1.2. Comparison 1 Oral or intramuscular penicillin versus control, Outcome 2 Streptococcal throat infections.

Study or subgroup	Penicillin n/N	Placebo / Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Feinstein 1966	30/82	30/79		0.96[0.65,1.44]
Padmavati 1973	192/523	207/471		0.84[0.72,0.97]



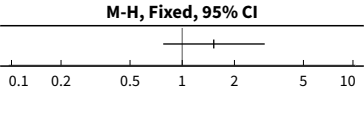
Analysis 1.3. Comparison 1 Oral or intramuscular penicillin versus control, Outcome 3 All Cause Mortality.

Study or subgroup	Penicillin n/N	Placebo / Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Padmavati 1973	41/523	30/471		1.23[0.78,1.94]



Analysis 1.4. Comparison 1 Oral or intramuscular penicillin versus control, Outcome 4 Mortality due to progress of heart failure or carditis.

Study or subgroup	Penicillin n/N	Placebo / Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Padmavati 1973	22/523	13/471		1.52[0.78,2.99]



Comparison 2. Intramuscular versus oral penicillin

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Rheumatic fever recurrences	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Streptococcal throat infections	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Intramuscular versus oral penicillin, Outcome 1 Rheumatic fever recurrences.

Study or subgroup	Intramuscular n/N	Oral n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Feinstein 1959	1/116	15/113		0.06[0.01,0.48]
Wood 1964	2/146	30/143		0.07[0.02,0.27]
Feinstein 1965	1/136	18/101		0.04[0.01,0.3]
Feinstein 1968	3/163	26/180		0.13[0.04,0.41]

Analysis 2.2. Comparison 2 Intramuscular versus oral penicillin, Outcome 2 Streptococcal throat infections.

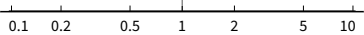
Study or subgroup	Intramuscular n/N	Orall n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Feinstein 1959	12/116	15/113		0.78[0.38,1.59]
Feinstein 1965	9/136	73/101		0.09[0.05,0.17]
Feinstein 1968	33/163	124/180		0.29[0.21,0.4]
Wood 1964	24/146	101/143		0.23[0.16,0.34]

Comparison 3. Two-weekly versus 4-weekly penicillin injections

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Rheumatic fever recurrences	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Streptococcal throat infections	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Two-weekly versus 4-weekly penicillin injections, Outcome 1 Rheumatic fever recurrences.

Study or subgroup	2-weekly injections n/N	4-weekly injections n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kassem 1996	24/190	41/170		0.52[0.33,0.83]



Analysis 3.2. Comparison 3 Two-weekly versus 4-weekly penicillin injections, Outcome 2 Streptococcal throat infections.

Study or subgroup	2-weekly injections n/N	4-weekly injections n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kassem 1996	38/190	57/170		0.6[0.42,0.85]

Comparison 4. Three-weekly versus 4-weekly intramuscular penicillin

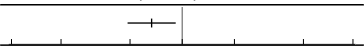
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Rheumatic fever recurrences	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Streptococcal throat infections	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4 Three-weekly versus 4-weekly intramuscular penicillin, Outcome 1 Rheumatic fever recurrences.

Study or subgroup	3-weekly injections n/N	4-weekly injections n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Lue 1996	9/124	16/125		0.57[0.26,1.23]

Analysis 4.2. Comparison 4 Three-weekly versus 4-weekly intramuscular penicillin, Outcome 2 Streptococcal throat infections.

Study or subgroup	3-weekly injections n/N	4-weekly injections n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Lue 1996	39/124	59/125		0.67[0.48,0.92]



ADDITIONAL TABLES

Table 1. Table of experts contacted

Name	Institution	Country
Dr Porfirio Nordet	Cardiovascular Disease Programme, WHO	Switzerland
Dr Thomas Nchinda	Global Health Forum, c/o WHO	Switzerland
Professor Edward L. Kaplan	University of Minesota Medical School	USA
Professor Walinjom FT Muna	Pan-African Society of Cardiology	Cameroon
Dr Peter Odhiambo	Kenya Cardiac Society	Kenya
Professor Oladipo O Akinkugbe	Nigeria Heart Foundation	Nigeria
Dr Albertino Damasceno	Faculty of Medicine, Eduardo Mondlane University	Mozambique
Professor Aly Ramsy	Egyptian Society of Cardiology	Egypt

Table 1. Table of experts contacted *(Continued)*

Professor PJ Comerford	Department of Cardiology, Groote Schuur Hospital	South Africa
Dr Edmund Brice	Tygerberg Hospital, University of Stellenbosch	South Africa
Dr SRA Zaher	Department of Paediatrics, University of Alexandria	Egypt
Professor S Padmavati	All India Heart Foundation	India
Professor KS Reddy	Cardiovascular Research Initiative, All India Institute of Medical Sciences	India
Professor HC Lue	Department of Paediatrics, National Taiwan University College of Medicine	Taiwan
Dr Rao Xuxu	Department of Cardiology and Cardiovascular Epidemiology, Guangdong Provincial Cardiovascular Institute	People's Republic of China
Dr Santiago V Guzman	Philippine Heart Centre	Philippine
Dr D Millard	Child Health Department, University of West Indies	Jamaica
Dr D Symmonds	Heart Foundation of Barbados	Barbados
Professor Aloyzio Achutti		Brazil

APPENDICES

Appendix 1. Search Strategies

CENTRAL on The Cochrane Library

1 MeSH descriptor RHEUMATIC FEVER explode all trees
2 RHEUMATIC*
3 CHOREA:ME
4 CHOREA*
5 RHD
6 RHEUMATISM
7 (#1 or #2 or #3 or #4 or #5 or #6)
8 MeSH descriptor PENICILLINS explode all trees
9 PENICILLIN*
10 ULTRACILLIN
11 PHENOXYMETHYLPENICILLIN*
12 PENICILIUM*
13 PENICILLIUM*
14 ORAPEN*
15 MeSH descriptor ANTIBIOTIC PROPHYLAXIS explode all trees
16 PROPHYLAXIS
17 (SECONDARY and PREVENT*)
18 (#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17)
19 (#7 and #18)

MEDLINE on Ovid

1 exp Rheumatic fever/
2 rheumati$.tw.
3 Chorea/
4 chorea$.tw.
5 rhd.tw.
6 exp Penicillins/

7 penicillin$.tw.
8 phenoxymethylpenicillin.tw.
9 Antibiotic prophylaxis/
10 prophylax$.tw.
11 or/1-5
12 or/6-10
13 11 and 12
14 randomized controlled trial.pt.
15 controlled clinical trial.pt.
16 Randomized controlled trials/
17 random allocation.sh.
18 double blind method.sh.
19 single-blind method.sh.
20 or/14-19
21 (animal not human).sh.
22 20 not 21
23 clinical trial.pt.
24 exp Clinical trials/
25 (clin$ adj25 trial$).ti,ab.
26 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab.
27 placebos.sh.
28 placebo$.ti,ab.
29 random$.ti,ab.
30 research design.sh.
31 or/23-30
32 31 not 21
33 32 not 22
34 comparative study.sh.
35 exp evaluation studies/
36 follow up studies.sh.
37 prospective studies.sh.
38 (control$ or prospectiv$ or volunteer$).ti,ab.
39 or/34-38
40 39 not 21
41 40 not (22 or 33)
42 22 or 33 or 41
43 13 and 42

EMBASE on Ovid

1 Rheumatic fever/
2 rheumati$.tw.
3 Chorea Minor/
4 chorea$.tw.
5 rhd.tw.
6 or/1-5
7 exp Penicillin Derivative/
8 penicillin$.tw.
9 phenoxymethylpenicillin.tw.
10 Antibiotic prophylaxis/
11 prophyla$.tw.
12 Secondary prevention/
13 or/7-12
14 6 and 13
15 random$.ti,ab.
16 factorial$.ti,ab.
17 (crossover$ or cross over$ or cross-over$).ti,ab.
18 placebo$.ti,ab.
19 (double$ adj blind$).ti,ab.
20 (singl$ adj blind$).ti,ab.
21 assign$.ti,ab.
22 allocat$.ti,ab.

23 volunteer$.ti,ab.
24 Crossover Procedure/
25 Double Blind Procedure/
26 Randomized Controlled Trial/
27 Single Blind Procedure/
28 or/15-27
29 28 and 14

LILACs on BIRME

rheumatic or reumática [Palavras] and penicillin$ [Palavras]

WHAT'S NEW

Date	Event	Description
15 January 2013	Review declared as stable	Authors no longer wish to update this review.

HISTORY

Protocol first published: Issue 3, 2000
Review first published: Issue 3, 2002

Date	Event	Description
29 June 2009	New search has been performed	Third update. The search was updated on 25th June 2009. No new studies were identified. The conclusions remain unchanged.
9 September 2008	Amended	Converted to new review format.
1 October 2007	New search has been performed	SECOND UPDATE Published Issue 4 2007 (October 2007) The search was updated to June 2007. One potential study was identified (Brick et al 1950), but excluded from the review because it does not meet the inclusion criteria, as stated in detail in the 'Excluded studies' section. Therefore, the conclusions of the review remain unchanged
1 July 2005	New search has been performed	FIRST UPDATE Published Issue 3 2005 (July 2005) In this update the authors re-ran the searches for randomised controlled trials up to February 2005. No new studies have been published since July 2000. The conclusions of the review remain unchanged.
24 April 2002	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

J Manyemba - Designed protocol, designed data extraction forms, developed search strategy, screened results, appraised papers, extracted data, entered, analysed and interpreted data, wrote first and subsequent drafts and coordinated the review.

B M Mayosi - Revised protocol, screened results, extracted data, appraised papers, revised second and final draft of the review. Updated review in April 2005.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Guy's, King's and St Thomas's School of Medicine. King's College Hospital. London, UK.
- Cardiac Clinic, Groote Schuur Hospital, Cape Town, South Africa.

External sources

- Cochrane Health Promotion and Pubic Health Field, Australia.

NOTES

Authors no longer wish to update this review.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Drug Administration Schedule; Injections, Intramuscular; Penicillins [*administration & dosage]; Recurrence; Rheumatic Fever [*prevention & control]; Streptococcal Infections [*prevention & control]

MeSH check words

Humans